REMARKS

Claims 1-7 and 11-14 and 26 are pending. Applicants have canceled claims 15-25 without acquiescence and without prejudice as they are drawn to a non-elected invention. Applicants have amended claims 4, 5, and 26 without prejudice and without acquiescence. Support for amendments to claim 4 can be found on page 19, line 31 to page 20, line 2. Applicants maintain the right to file a continuation and/or divisional application on any canceled or amendment subject matter. No new matter has been added.

The issues outstanding in this application are as follows:

- Priority
- Objections to Specification
- Objections to the Sequence Listing Statement
- Claims 1-7, 11-14 and 26 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with written description requirement.
- Claims 1-7, 11-14 and 26 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing no reasonably providing enablement.
- Claim 4 is rejected under 35 U.S.C. § 112 as allegedly being indefinite.

Applicant respectfully traverses the outstanding objections and rejections, and applicant respectfully requests reconsideration and withdrawal thereof in light of the amendments and remarks contained herein.

I. Priority

The Examiner has indicated that a certified copy of the GB0016172.9 application has not been filed. In fact, certified copies of both priority documents were timely filed during the International phase. In support of this, a copy of a Form PCT/IB/304 dated 22 November 2000 indicating that certified copies of both priority documents were received by the

International Bureau of WIPO on 1 September 2000, i.e. within 16 months of the earliest priority date of 30 July 1999.

II. Specification Objection

Claims 5 and 26 have been objected to because of informalities. In order to advance the prosecution of this application, Applicant has amended claims 5 and 26 as requested by the Examiner without prejudice and without acquiescence.

III. Sequence listing Statement

The Examiner has indicated that the Sequence listing statement pursuant to 37 CFR 1.823(b) is not complete. Applicants assert that there were no amendment made to the sequence listing. In fact, the Patent Office required the applicants to submit a sequence listing because the application contained sequences. Thus, Applicants complied with this requirement. The Statement that was submitted on October 21, 2002 was filed in error and the Statement should be submitted under 37 CFR 1.821(f), of which a new statement is submitted herewith.

IV. 35 U.S.C. § 112, first paragraph

A. Written Description

Claims 1-7, 11-14 and 26 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants traverse.

The Examiner argues that the specification fails to provide adequate written description for a "functional variant" of a nitric oxide synthase (NOS). Applicants respectively traverse this rejection. Applicants remind the Examiner that 35 USC § 112 states:

> "The specification shall contain a written description of the invention, and of the manner and the process of making it and using it, in such full, clear, concise, and exact terms to enable any person skilled in the art to

which it pertains, or which it is most nearly connected to make use and use the same..."

This requirement ensures that, as of the filing date, the inventors have conveyed, with reasonable clarity, to those skilled in the art that they were in possession of the subject matter of the claims. The written description requirement does not, however, compel the Applicant to describe exactly the subject matter claimed, instead the description must clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed. Applicants respectively submits that, in the circumstances, these requirements have been satisfied and that there is adequate description of all the claimed elements.

As the Examiner points out, a "functional variant" of a NOS is defined at the third full paragraph on page 10 of the specification as "any polypeptide which demonstrates an NOS activity". Clearly, "any NOS activity" refers to any polypeptide capable of synthesizing nitric oxide

(NO) from arginine. A skilled person would thus understand that the term "functional variant" encompasses the use of any polynucleotide encoding any polypeptide capable of synthesizing nitric oxide.

The description of the instant application, at page 10, line 13 to page 11, line 25, describes in detail how such functional variants may be generated. Example 1 then specifically describes the generation of NOS expressing plasmids using a 4164bp fragment of human iNOS, a 5KB fragment of human nNOS and the wild-type human eNOS sequence. The Examples thus exemplify the use of three different types of NOS. There is no reason to doubt that further constructs could be made with other "functional variants" of a NOS on the basis of the guidance provided in the specification.

In particular, it would be well within the ordinary skill in the art to determine whether any given polynucleotide encodes a polypeptide which is functional variant of a NOS, for example by expressing such a polypeptide recombinantly and then determining whether it is capable of producing nitric oxide from arginine. In can be seen therefore that those of ordinary skill in the art would know how to determine whether any given variant of a NOS is a functional variant in accordance with the invention.

It is of course well settled that patent Applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Vaeck* 947F.2D 488, 496 (FED.CIR.1991) (quoting In re Angstade, 537F.2D 498,502-03 (CCPA 1976)). In view of this, Applicants respectively submit that they have provided a full written disclosure to enable one skilled in the art to make and use a "functional variant" as required by the claims. Applicants therefore respectfully request that the examiner withdraw the rejection of claims 1 to 7, 11 to 14 and 26 under 35 USC § 112, first paragraph.

B. Enablement

Claims 1-7, 11-14 and 26 stand rejected under 3 U.S.C. § 112, first paragraph, as being unpatentable for failure to comply with the enablement requirement. Applicants traverse.

In more detail, the Examiner argues that the use of encapsulated cells in general remains at an early stage of development, that the short half-life and limited range of NO suggests that the claimed microcapsules would have an effect of only a few cell diameters, that therapeutic use of the promoters referred to in the instant invention remain under investigation and that xeongraft cancer models are poor predictors of clinical efficacy. The Examiner has referred to the Orive, Murphy, Graham and Gromeier references, in particular, in support of these key assertions.

It is submitted though that each of these assertions is rebutted by the information provided in the instant application or, with respect, is not relevant. For example, the fact that the promoters used in the specification may or may not be sanctioned for clinical use is not an issue that is relevant to enablement as the requirements for regulatory approval are wholly separate from those for patentability.

Applicants have provided teachings in the specification which are adequate to enable one of ordinary skill in the art to practice the claimed invention throughout its scope. Specifically, a person skilled in the art is taught by the specification how to prepare the microcapsules of the invention. Applicants then teach that such microcapsules can be used in therapy. Thus, one skilled in the art is provided with information in the specification to make

the claimed microcapsules and to use such microcapsules in therapy, in particular in the treatment of conditions wherein deficient nitric oxide is implicated.

Assuming for the moment that the Examiner has met the burden of providing reasons for raising a rejection of lack of enablement, and taking into consideration the Examiner's statements with respect to undue experimentation, Applicants maintain that the claimed invention is enabled. Determination of undue experimentation follows from the analysis of the eight Wands factors. *In re Wands* 858 F.2d 731, 737, 740, 8 USPQ2d 1400,1404, 1407 (Fed. Cir. 1998). Applicants maintain that full consideration of each and all of the Wands factors, in view of the state of the art at the time of filing, leads one to the reasonable conclusion that practice of the invention would not require undue experimentation.

In particular, with respect to the presence of Examples, the court in Wright stated that "Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *In re Wright* at 1561 citing *In re Marzochhi* 439 F.2d 220, 223, 169 USPQ 367, 369 (C.C.P.A. 1971). Applicants have provided not only broad terminology which is readily understandable to one of ordinary skill in the art, but also illustrative examples of the treatment of a cancer using the claimed microcapsules.

The enablement requirement requires that Applicants must provide a specification that enables a person reasonably skilled in the art to make and use the claimed invention without undue experimentation. The fact that some experimentation may be employed, however, does not make it undue if a person of skill in the art typically engages in such experimentation. This is because the prohibition is against "undue experimentation," not merely "experimentation". *In re Angstadt*, 537 F.2d, 498, 502-03 (CCPA 1976).

Requiring the applicants to provide an exhaustive experimental study into any and all possible embodiments would discourage disclosure of discoveries and is in direct contradiction of the principles underlying 35 USC § 112. *See, e.g., Rohm & Haas Co. v Dawson Chemical Co.*, 217 USPQ 515, 563-64 (S.D. Tex. 983), rev'd on other grounds, 220 USPQ 289 (Fed. Cir. 1983, cert. denied, 469 U.S. 851 (1984).

In the circumstances, it is submitted that the quantity of experimentation needed to use of the invention over the whole of the scope of the claims is not unreasonable for one of ordinary skill in the art. Indeed, Applicants maintain that persons of ordinary skill in the art routinely engage in such experimentation.

On the basis of the foregoing arguments, Applicants respectfully request that the Examiner withdraw the rejection of claims 1 to 7, 11 to 14 and 26 under 35 USC § 112, first paragraph.

V. 35 U.S.C. § 112, second paragraph

Claim 4 is rejected under 35 U.S.C. § 112 as being indefinite. Applicants traverse.

In order to advance the prosecution of the present application, Applicants have amended claim 4 to clarify the scope without prejudice and without acquiescence. In view of this amendment, Applicants request that the rejection be withdrawn.

CONCLUSION

In view of the above arguments, Applicants respectfully request that the rejection be withdrawn.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 06-2375, under Order No. 10201564 from which the undersigned is authorized to draw.

Dated: January 10, 2005

Respectfully submitted,

By _____

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